Medical and Pediatric Oncology 28:444–450 (1997)

Phase I Trial of Subcutaneous Interleukin-1α in Children With Malignant Solid Tumors

Wayne L. Furman, MD,[1,3]* Xiaolong Luo, PhD,[2] Diane Fairclough, DrPH,[2] Leslie Garrison, MD,[5] Neyssa Marina, MD,[1,3] Charles B. Pratt, MD,[1,3] Archie Bleyer, MD,[4] and William H. Meyer, MD[1,3]

Interleukin-1α (IL-1α) is myeloprotective in a variety of animal models of cancer chemotherapy and is similarly beneficial in adults treated with carboplatin, 5-fluorouracil, and after autologous bone marrow transplantation. There are no trials of this agent in children. Our purpose was to determine the toxicity and maximum tolerated dose (MTD) of recombinant human interleukin-1α (rhuIL-1α) in children with solid tumors receiving intensive cancer chemotherapy and to evaluate its myeloprotective effects. Cohorts of patients received rhuIL-1α in doses of 0.1–10 μg/m² for 4 days by subcutaneous injection prior to ICE chemotherapy (ifosfamide, 2 g/m²/day × 3, carboplatin targeted to an area under the curve of 8 mg/ml × min on day 1, and etoposide, 100 mg/m² daily for 3 days). Patients were randomized to receive rhuIL-1α before either the first or second course of therapy. After the MTD of rhuIL-1α was determined, an additional group of patients received rhuIL-1α at that dose immediately following ICE chemotherapy. The dose-limiting toxicities of rhuIL-1α in the 27 children tested comprised systemic symptoms of fever, chills, headache, and hypotension. The MTD was 3 μg/m²/day. There were no differences in chemotherapy-induced hematologic toxicity with increasing doses of rhuIL-1α or in comparisons before or after ICE chemotherapy. Although rhuIL-1α can be given safely to children receiving myelosuppressive chemotherapy, clinical usefulness would mandate a significant hematopoietic benefit in view of the troublesome side effects identified. We saw no evidence of a hematoprotective effect. Med. Pediatr. Oncol. 28:444–450, 1997.

Key words: phase I trial; interleukin-1; children; solid tumors

INTRODUCTION

Increasing dose intensity is an important strategy in attempting to improve survival for children with malignant solid tumors [1]. Dose escalation is limited by myelosuppression, which may be ameliorated to varying extents with hematopoietic growth factors. However, none of the currently approved colony-stimulating factors significantly affects platelet recovery [2–7]. A hemopoietin with the ability to accelerate both platelet and granulocyte recovery would be of significant benefit. Recent evaluations of interleukin-1 (IL-1) in adults with cancer [8–12] have shown some promise, but there have been no previous clinical trials of this cytokine in children.

Interleukin-1α (IL-1α) and IL-1β are polypeptides that bind to the same receptor and have similar biologic activities including effects on immune system function and on the regulation of hematopoiesis [13,14]. In murine models, pretreatment with IL-1α protects against the otherwise lethal myelotoxic effects of chemotherapy with a variety of agents including 5-fluorouracil [10,15], doxorubicin [16,17], cyclophosphamide [18,19], cisplatin, and carboplatin [15]. On the basis of these data, as well as promising early findings in studies of adults [9–12], we developed a phase I/II trial to evaluate the safety, maximum tolerated dose (MTD), and myeloprotective effects of recombinant human IL-1α (rhuIL-1α) in children receiving intensive multiagent chemotherapy for recurrent malignant solid tumors.

PATIENTS AND METHODS

Between June 1991 and July 1993, 28 children (≤21 years of age) with refractory solid tumors or tumors for which no standard therapy was available were entered on

Dr. Fairclough is now at the Department of Biostatistics, AMC Cancer Research Center, Denver, CO.

Dr. Marina is now at the Department of Pediatrics, Stanford University School of Medicine, Stanford University Medical Center, Stanford, CA.

[1]Department of Hematology-Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee; [2]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, Tennessee; [3]Department of Pediatrics, University of Tennessee, College of Medicine, Memphis, Tennessee; [4]University of Texas M.D. Anderson Cancer Center, Houston, Texas; [5]Immunex Corporation, Seattle, Washington.

*Correspondence to: Dr. Wayne L. Furman, Department of Hematology-Oncology, St. Jude Children's Research Hospital, 332 N. Lauderdale, Memphis, TN 38105-2794.

Received 17 July 1996; Accepted 26 September 1996

a clinical trial of chemotherapy with ifosfamide, carboplatin, and etoposide (ICE), preceded by escalating doses of rhuIL-1α. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of at least 2, a life expectancy of at least 8 weeks, adequate renal and liver function (serum creatinine <2.0 mg/dl; bilirubin <2.0 mg/dl; alkaline phosphatase ≤3 times normal), absolute neutrophil count (ANC) ≥1,000/μl, packed red cell volume >29%, and platelet count ≥100,000/μl. This trial was approved by the St. Jude Children's Research Hospital Institutional Review Board, and written informed consent was obtained from patients, parents, and/or guardians, as appropriate.

Clinical and Laboratory Monitoring

Before enrollment in the study, patients underwent complete physical examinations and laboratory tests, including complete blood cell counts with differential, reticulocyte count, serum chemistry and coagulation profiles, urinalysis, estimation of glomerular filtration rate (GFR) by ^{99m}Tc-DTPA plasma clearance studies, and tumor assessment with appropriate diagnostic imaging studies. During each course of treatment, blood counts were performed at least 3 times weekly and serum chemistries were monitored weekly. Throughout the study period, patients were systematically evaluated for evidence of toxicity (rated using the NCI Common Toxicity Criteria), fever, need for blood product support, and signs of infection.

Patients who had an ANC <500/μl and fever (oral temperature >38.3°C, or a temperature >38°C for longer than 1 hr) were hospitalized and treated with broad-spectrum antibiotics. For data analysis, the duration of hospitalization was defined as the interval from admission to the point when the patient had remained afebrile for longer than 48 hr and all antimicrobials (except trimethoprim/sulfamethoxazole) were discontinued. Platelet transfusions were given only when the platelet count was ≤10,000/μl, unless there was clinically significant bleeding. Red blood cell transfusions were given as clinically indicated.

Study Design

In our trials using ICE chemotherapy, carboplatin doses are based on an estimate of carboplatin clearance adjusted to body surface area, determined by a previously described equation [20]. Carboplatin is eliminated primarily by glomerular filtration, and individualized dosing based on the GFR, estimated by ^{99m}Tc-DTPA plasma clearance, reliably correlates with toxicity, particularly thrombocytopenia [20,21]. In this trial, carboplatin was administered intravenously on day 1 to achieve a targeted systemic exposure or area under the curve (AUC) of 8 mg/ml × min. Ifosfamide (2 g/m^2/day) and etoposide (100 mg/m^2/day) were given on days 2, 3, and 4. Ifosfamide administration was followed immediately by Mesna uroprotection (500 mg/m^2), which was repeated 3 and 6 hr later. Doses of chemotherapy were not modified in subsequent cycles; if a patient's GFR increased or decreased by more than 15%, the patient was taken off the study.

Subcutaneous administration of rhuIL-1α (produced in *Escherichia coli* and supplied by Immunex Corporation, Seattle, WA, as a lyophilized powder in vials containing 100 μg rhuIL-1α protein, 40 mg mannitol USP, 10 mg sucrose NF, and 1.2 mg Tris USP) was started before the course of chemotherapy was initiated and continued daily for 4 days. Cohorts of 4–5 patients were studied at rhuIL-1α dosage levels of 0.1, 0.3, 1.0, 3.0, and 10.0 μg/m^2/day. Within dose cohorts, patients were randomly assigned to receive rhuIL-1α with either the first or second cycle of chemotherapy. In these patients, the 4 day ICE chemotherapy regimen was started the day after the last dose of rhuIL-1α. After the MTD was determined, 5 additional patients received rhuIL-1α at the defined dosage daily for 4 days beginning the day after the last day of ICE chemotherapy (Fig. 1).

Statistical Methods

Outcome measures used to evaluate the hematoprotective effects of rhuIL-1α included ANC nadir, platelet nadir, number of platelet transfusions, number of packed red blood cell (PRBC) transfusions, duration of grade 4 neutropenia, duration of thrombocytopenia (platelet counts <50,000/μl and <20,000/μl), and duration of hospitalization for febrile neutropenia. These outcome measures were assumed to be independent of cycle of chemotherapy. Within-subject differences were compared using Wilcoxon's signed rank test for cycles with and without rhuIL-1α. Descriptive statistics were calculated for all outcome measures. The Kruskal-Wallis test [22] was used to compare among groups.

We had a sufficient power (80%, $\alpha = 0.05$) to detect a difference in the timing of administration of rhuIL-1α (before or after ICE chemotherapy) if there is a probability of at least 0.91 that the median duration of neutropenia or thrombocytopenia is longer for a patient in one group than for a patient in the other group [23]. For patients treated at the MTD compared to other doses, we had sufficient power (80%, $\alpha = 0.05$) to detect a difference if there is a probability of at least 0.86 that the median duration of thrombocytopenia or neutropenia is longer for a patient in one group than for a patient in the other group [23].

The dose-response effect across dose levels was tested using a distribution-free test for ordered alternatives (Jonckheere) [24]. Since most published adult trials [8–10,12,25] describe a dose-response effect on neutrophils and platelets with IL-1, a one-sided test was used.

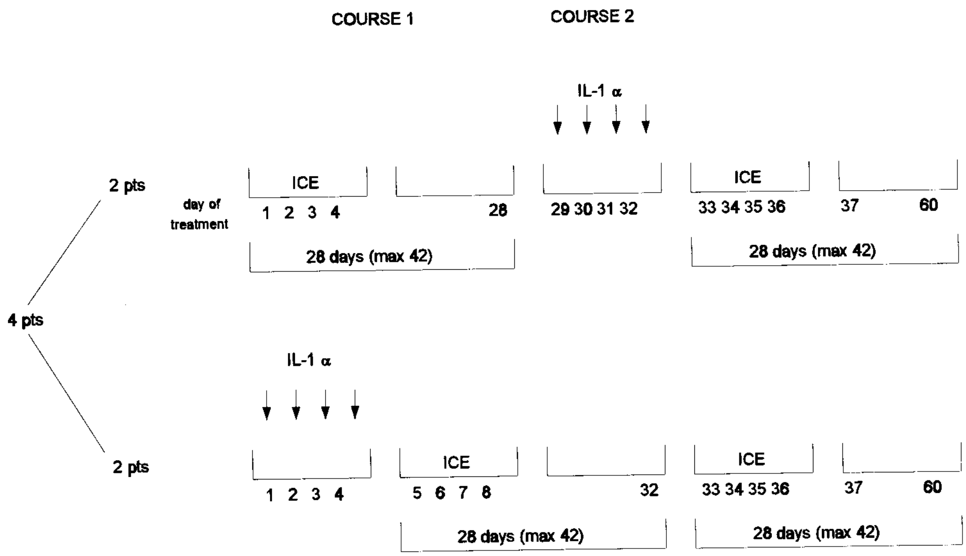

Fig. 1. Schema of treatment. Patients were randomized at each dose level to receive rhuIL-1α by daily subcutaneous injection for 4 consecutive days prior to the first (n = 2) or second (n = 2) cycle of chemotherapy. At the MTD an additional 5 patients received rhuIL-1α daily for 4 days beginning the day after the last day of ICE chemotherapy.

RESULTS

Of the 28 patients enrolled in this study, 1 (assigned to receive 3.0 μg/m^2 of rhuIL-1α after the second cycle of ICE chemotherapy) was withdrawn from the study by his parents before receiving any rhuIL-1α. Table I lists the characteristics and prior treatment of the 27 patients who received at least one dose of rhuIL-1α and are evaluable for toxicity. The median age at study enrollment was 8 years (range 5 months to 21 years). Twenty-two children had full performance status (ECOG 0). The majority of patients had received prior multiagent chemotherapy (median 4 drugs), with autologous bone marrow transplantation in 3 cases; 15 of these 21 patients had also received radiation therapy. Four children had received radiation therapy only and two had no prior therapy.

TABLE I. Characteristics of the 27 Children Treated With ICE Plus IL-1α

Characteristic	No. of patients
Diagnosis	
Neuroblastoma	9
Brain tumor	4
Ewing's sarcoma	2
Osteosarcoma	2
Non-rhabdo soft tissue sarcoma	6
Rhabdomyosarcoma	1
Wilms' tumor	1
Germ cell tumor	2
Age (years)	
0–2	2
2–10	15
10–21	10
Sex	
Male	17
Female	10
Performance status (ECOG)	
0	22
1	5
2	0
Prior treatment	
Radiation	18
Chemotherapy[a]	21
Autologous bone marrow transplant	3
No prior treatment	2

[a]Previous chemotherapy included a median of 4 agents (range 0–8).

Clinical Tolerance of RhuIL-1α

Most patients had fever (n = 26) and chills (n = 20) associated with rhuIL-1α. Headaches were also frequent (n = 12) (Table II). Eleven patients had local erythema and tenderness at the injection site. Grade 1 or 2 hypotension was seen in 14 patients, of whom 4 were given fluid boluses. One required low-dose pressor support after the second dose (1 μg/m^2/day); pressors were discontinued the next day and he received further rhuIL-1α without problems.

Three patients received an incomplete course of rhuIL-1α. A 2-year-old with recurrent medulloblastoma developed tachycardia and ascites after one dose (0.3 μg/m^2). Further evaluation showed that these symptoms were secondary to progressive disease, with malignant cells in the peritoneal fluid. A 9-year-old child with medulloblastoma had mild systemic symptoms (fever and chills) after a single 3.0 μg/m^2 dose and was taken off the study at the parent's request. At the 10 μg/m^2 dose, a 17-year-old patient with a soft tissue sarcoma experienced a significant drop in blood pressure, beginning about 4 hr after the first injection. He required pressor

TABLE II. Side Effects in 27 Children Treated With IL-1α*

	Dose (μg/m²/day)					
Side effect	0.1 (n = 4)	0.3 (n = 4)	1.0 (n = 5)	3.0 (n = 4)	10.0[a] (n = 4)	3.0 (post-ICE) (n = 5)
Fever	4	4 (2)	5 (2)	4 (1)	4 (1)	5 (3)
Chills	0	2	5 (1)	4	4 (1)	5 (2)
Headache	2	2	4	1	3	0
Hypotension	0	3	3 (1)	3	3 (1)	4
Hypertension	0	0	1	0	0	0
Tachycardia	0	2	4	2	3	3
Local reaction	1	1	1	2	3	3
Rash	1	0	0	0	0	0
Nausea	0	1	0	1	1	0
Vomiting	0	0	1	2	3	2
Bone pain	0	2	2	0	0	0
Sleepiness or hallucinations	0	1	0	0	1	1 (1)

*Numbers in parentheses are instances of grade 3 or 4 toxicity.
[a]Dose-limiting toxicity was defined by significant systemic symptoms of fever (one with hallucinations), chills, and hypotension.

support with dopamine for 2 days and was taken off the study.

In addition to the 17-year-old described above at the 10 μg/m² dose, another patient at this dose required significant fluid boluses to maintain blood pressure. All 4 patients at this dose experienced significant rigors; 1 patient was grade 3. Coincident with fever and rigors, 1 child also had significant hallucinations. All systemic toxicities (except for the hypotension noted above) resolved within hours of the last injection. Thus, dose-limiting toxicity was defined at the 10.0 μg/m² dose level by hypotension requiring treatment (2 of 4 patients) and significant systemic symptoms (fever, chills, and headache) in all patients treated at this level.

Hematologic Effects

Of the 27 patients evaluable for toxicity, 19 had two full courses of ICE therapy and were included in the intrapatient analysis of hematologic effects. Five other patients received only one evaluable course of therapy and are included in the cohort comparisons. Of these 5, the inevaluable courses were due to insufficient complete blood counts done (1 each at the 0.3 and 3.0 μg/m² dose levels), and 3 did not receive two full courses of ICE chemotherapy because of progressive disease, parental refusal, and prolonged myelosuppression after an episode of sepsis. An additional 3 patients (described above) did not receive a full 4 day course of rhuIL-1α.

In 19 patients who had one course of ICE with and one without rhuIL-1α, no conclusive intrapatient differences were noted in cycles with or without rhuIL-1α (data not shown). We therefore combined dose cohorts to identify any dose-response effect and to evaluate any differences in outcome measures for administration of rhuIL-1α before vs. after ICE chemotherapy.

Granulocyte Response

The effect of increasing doses of rhuIL-1α on the duration of grade 4 neutropenia is shown in Table III. The median duration of neutropenia was shortest at the 0.1 μg/m² dose (four evaluable courses). We found no significant differences in comparisons with other dose levels (Kruskal-Wallis test) or with courses in which no rhuIL-1α was given (Wilcoxon's signed rank test). However, when these data were examined using the Jonckheere test [24] for trends over the ordered dose levels, the lower doses of IL-1 resulted in a more rapid recovery of severe neutropenia ($P = 0.039$).

The time of IL-1 administration (pre- or postchemotherapy) was unrelated to the duration of neutropenia. Although rhuIL-1α at lower doses may have had some effect on the duration of grade 4 neutropenia, there was no effect on hospitalization for febrile neutropenia (medians of various doses ranged from 0 to 7 days; $P = 0.51$) or of intravenous antibiotic therapy (medians of various doses ranged from 0 to 12 days; $P = 0.44$; data not shown).

Platelet Response

There was no discernible improvement in duration of grade 3 (<50,000/μl; data not shown) or more severe thrombocytopenia (<20,000/μl; Table III) with increasing doses of rhuIL-1α, and no apparent difference for administration before or after chemotherapy. There was no discernible dose or schedule effect on the numbers of platelet or PRBC transfusions (Table III).

DISCUSSION

The purpose of this study was to define the clinical safety and MTD of rhuIL-1α in children receiving inten-

TABLE III. Effect of IL-1α on the Hematologic Toxicity of ICE Chemotherapy

		Toxicity			
		Median days (range)		No. of transfusions	
Comparison	No. of cycles	Neutropenia (<500/μl)	Thrombocytopenia (<20,000/μl)	PRBCs	Platelets
Dose of IL-1α (μg/m²/day)					
0	21	17 (3–35)	4 (0–19)	2 (0–5)	5 (0–13)
0.1	4	11.5 (8–14)	1.5 (0–4)	2 (0–4)	4.5 (0–11)
0.3	2	18 (9–27)	5 (2–8)	3 (3–3)	12 (6–18)
1	5	16 (13–20)	7 (2–13)	2.5 (2–5)	6 (3–10)
3	8	15 (11–37)	6.5 (0–29)	1.5 (0–22)	4 (0–51)
10	3	21 (17–21)	2 (0–13)	2 (0–2)	4 (0–8)
All doses					
After ICE	5	24 (11–37)	10 (0–29)	2 (1–4)	7 (2–14)
Before ICE	17	15 (8–27)	3 (0–13)	2 (0–22)	6 (0–51)
Both schedules					
3 μg/m²	8	15 (11–37)	6.5 (0–29)	1.5 (0–22)	4 (0–51)
All other doses	14	15.5 (8–27)	2.5 (0–13)	2.0 (0–5)	6 (0–18)

P = not significant.

sive chemotherapy and to provide preliminary indications of hematoprotective effects. Treatment for 4 consecutive days was tolerated in doses up to 3 μg/m²/day. Most patients experienced fever, chills, and headache soon after treatment but these symptoms generally resolved within hours. Hypotension, seen in about half of these children treated, was manageable with close observation or moderate increases in intravenous fluids in most cases. At the 10 μg/m² dose, severe systemic symptoms of high fever >40°C, occasionally with hallucinations, significant rigors, and headache, occurred in all 4 patients. These troublesome symptoms along with significant hypotension requiring increases in intravenous fluids, fluid boluses, or pressor support precluded further dose escalation.

Studies in murine systems have documented the hematoprotective effects of IL-1 against the lethal toxicities of high-dose radiation therapy [19,26] and several chemotherapeutic agents [16–19,27]. Data from clinical trials in adults suggest that IL-1 may improve platelet recovery after high-dose carboplatin [9,12] or 5-fluorouracil [10] and may improve hematopoietic recovery, reduce infection, and improve survival after autologous bone marrow transplantation [11,25]. It therefore seemed reasonable to expect some benefit from rhuIL-1α in children receiving intensive ICE chemotherapy for malignant solid tumors.

Despite these impressive findings in both animal models and adults treated with chemotherapy, our data provide only a suggestion of modest benefit in duration of severe neutropenia, possibly at the lowest dose levels of rhuIL-1α (Table III). The reasons for the disparity of effects of rhuIL-1α between adults and children are unclear. The heterogeneous nature of our patient population with their variable prior treatment histories makes conclusions about the hematopoietic effects of rhuIL-1α difficult to draw. It is possible that these children are more heavily pretreated, resulting in less than normal marrow reserves. Also the intensity of ICE chemotherapy may preclude the demonstration of a possible modest benefit. Finally, dose and schedule of rhuIL-1α may have resulted in stem cell exposure insufficient to maximize rhuIL-1α's effect on megakaryopoiesis.

With regard to standard chemotherapeutic agents a generally accepted principle has been that ''more is better''; however, with most biologic agents such as IL-1, this is likely not the case. In fact, for most biologics, there is a bell-shaped curve in which there is an ''optimal biologic dose'' that gives a peak response of biological function [28]. Dosages more or less than this ''optimal biologic dose'' will result in a loss of activity. For an agent such as IL-1, with such pleiotropic activities, the maximal effect of a particular biologic activity (e.g., effect on neutrophils) is very likely within a very narrow concentration and time window and depends on dose, schedule, and timing of administration. A different dose or schedule may be needed to maximize effects on platelets, for example. This effect has been seen in several animal models [16,19], and our data suggest that the 0.1 μg/m² rhuIL-1α dose had the optimal effect on duration of grade 4 neutropenia. These data highlight some of the challenges in determining the ''optimal biologic dose'' of an agent such as IL-1α with such diverse effects as well as underscore some of the problems in translating information from animal models into the clinic.

The side effects of rhuIL-1α at doses ≤3.0 μg/m² were manageable but far from trivial, and would be acceptable only if significant benefit could be anticipated. Clearly the margin between clinical benefit and unacceptable toxicity in humans is very narrow. Given the lack of benefit of rhuIL-1α on thrombopoiesis and erythropoiesis, further development of rhuIL-1α in children

will require additional preclinical investigation to understand how best to manipulate the narrow beneficial therapeutic window.

Although our data would suggest that the use of rhuIL-1α as a hemopoietin may be limited, its use as a biologic response modifier, in combination with standard chemotherapeutic agents, is still being examined [29–32]. Additionally, new data on the use of nitric oxide synthase inhibitors to prevent the troublesome side effects of IL-1 may open up new avenues of clinical investigation [33].

ACKNOWLEDGMENTS

We are indebted to Loraine Avery and Joanna Hwang for their assistance in data management and Christy Wright for her editorial review. This work was supported in part by National Cancer Institute grants P30 CA-21765 and CA-23099, by a grant from Immunex Corporation, and by the American Lebanese Syrian Associated Charities (ALSAC).

REFERENCES

1. Crist WM, Kun LE: Common solid tumors of childhood (see comments). N Engl J Med 324:461–471, 1991.
2. Crawford J, Ozer H, Stoller R, Johnson D, Lyman G, Tabbara I, Kris M, Grous J, Picozzi V, Rausch G, Smith R, Gradishar W, Yahanda A, Vincent M, Stewart M, Glaspy J: Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 325:164–170, 1991.
3. Furman WL, Fairclough DL, Huhn RD, Pratt CB, Stute NS, Petros WP, Evans WE, Bowman LC, Douglass EC, Santana VM, Meyer WH, Crist WM: Therapeutic effects and pharmacokinetics of recombinant human granulocyte-macrophage colony-stimulating factor in childhood cancer patients receiving myelosuppressive chemotherapy. J Clin Oncol 9:1022–1028, 1991.
4. Nemunaitis J, Singer JW, Buckner CD, Hill R, Storb R, Thomas ED, Appelbaum FR: Use of recombinant human granulocyte-macrophage colony-stimulating factor in autologous marrow transplantation for lymphoid malignancies. Blood 72:834–836, 1988.
5. Brugger W, Frisch J, Schulz G, Pressler K, Mertelsmann R, Kanz L: Sequential administration of interleukin-3 and granulocyte-macrophage colony-stimulating factor following standard-dose combination chemotherapy with etoposide, ifosfamide, and cisplatin. J Clin Oncol 10:1452–1459, 1992.
6. Ganser A, Lindemann A, Seipelt G, Ottmann OG, Herrmann F, Eder M, Frisch J, Schulz G, Mertelsmann R, Hoelzer D: Clinical effects of recombinant human interleukin-3. Am J Clin Oncol 14(Suppl 1):S51–S63, 1991.
7. Furman WL, Crist WM: Biology and clinical applications of hemopoietins in pediatric practice. Pediatrics 90:716–728, 1992.
8. Smith JW, Urba WJ, Curti BD, Elwood LJ, Steis RG, Janik JE, Sharfman WH, Miller LL, Fenton RG, Conlon KC: The toxic and hematologic effects of interleukin-1 alpha administered in a phase I trial to patients with advanced malignancies. J Clin Oncol 10: 1141–1152, 1992.
9. Vadhan-Raj S, Kudelka AP, Garrison L, Gano J, Edwards CL, Freedman RS, Kavanagh JJ: Effects of interleukin-1 alpha on carboplatin-induced thrombocytopenia in patients with recurrent ovarian cancer. J Clin Oncol 12:707–714, 1994.
10. Crown J, Jakubowski A, Kemeny N, Gordon M, Gasparetto C, Wong G, Sheridan C, Toner G, Meisenberg B, Botet J, et al: A phase I trial of recombinant human interleukin-1 beta alone and in combination with myelosuppressive doses of 5-fluorouracil in patients with gastrointestinal cancer. Blood 78:1420–1427, 1991.
11. Nemunaitis J, Appelbaum FR, Lilleby K, Buhles WC, Rosenfeld C, Zeigler ZR, Shadduck RK, Singer JW, Meyer W, Buckner CD: Phase I study of recombinant interleukin-1 beta in patients undergoing autologous bone marrow transplant for acute myelogenous leukemia. Blood 83:3473–3479, 1994.
12. Smith JW, Longo DL, Alvord WG, Janik JE, Sharfman WH, Gause BL, Curti BD, Creekmore SP, Holmlund JT, Fenton RG: The effects of treatment with interleukin-1 alpha on platelet recovery after high-dose carboplatin. N Engl J Med 328:756–761, 1993.
13. Dinarello CA: Interleukin-1 and interleukin-1 antagonism. Blood 77:1627–1652, 1991.
14. Dinarello CA: Biologic basis for interleukin-1 in disease. Blood 87:2095–2147, 1996.
15. Damia G, Komschlies KL, Futami H, Back T, Gruys ME, Longo DL, Keller JR, Ruscetti FW, Wiltrout RH: Prevention of acute chemotherapy-induced death in mice by recombinant human interleukin 1: Protection from hematological and nonhematological toxicities. Cancer Res 52:4082–4089, 1992.
16. Eppstein DA, Kurahara CG, Bruno NA, Terrell TG: Prevention of doxorubicin-induced hematotoxicity in mice by interleukin 1. Cancer Res 49:3955–3960, 1989.
17. Lynch DH, Rubin AS, Miller RE, Williams DE: Protective effects of recombinant human interleukin-1 alpha in doxorubicin-treated normal and tumor-bearing mice. Cancer Res 53:1565–1570, 1993.
18. Futami H, Jansen R, MacPhee MJ, Keller J, McCormick K, Longo DL, Oppenheim JJ, Ruscetti FW, Wiltrout RH: Chemoprotective effects of recombinant human IL-1 alpha in cyclophosphamide-treated normal and tumor-bearing mice. Protection from acute toxicity, hematologic effects, development of late mortality, and enhanced therapeutic efficacy. J Immunol 45:4121–4130, 1990.
19. Castelli MP, Black PL, Schneider M, Pennington R, Abe F, Talmadge JE: Protective, restorative, and therapeutic properties of recombinant human IL-1 in rodent models. J Immunol 140:3830–3837, 1988.
20. Marina NM, Rodman J, Shema SJ, Bowman LC, Douglass E, Furman W, Santana VM, Hudson M, Wilimas J, Meyer W, et al: Phase I study escalating targeted doses of carboplatin combined with ifosfamide and etoposide in children with relapsed solid tumors. J Clin Oncol 11:554–560, 1993.
21. Calvert AH, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E: Carboplatin dosage: prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748–1756, 1989.
22. Lehmann EL, D'Abrera HJM (eds): ''Nonparametrics: Statistical Methods Based on Ranks.'' San Francisco: Holden-Day, 1975.
23. Noether GE: Sample size determination for some common nonparametric tests. J Am Stat Assoc 82:645–647, 1987.
24. Hollander M, Wolfe DA: ''Nonparametric Statistical Methods.'' New York: John Wiley & Sons, 1973.
25. Weisdorf D, Katsanis E, Verfaillie C, Ramsay NK, Haake R, Garrison L, Blazar BR: Interleukin-1 alpha administered after autologous transplantation: A phase I/II clinical trial. Blood 84: 2044–2049, 1994.
26. Neta R, Oppenheim JJ: Cytokines in therapy of radiation injury. Blood 72:1093–1095, 1988.
27. Fibbe WE, van der Meer JW, Falkenburg JH, Hamilton MS, Kluin PM, Dinarello CA: A single low dose of human recombinant

interleukin 1 accelerates the recovery of neutrophils in mice with cyclophosphamide-induced neutropenia. Exp Hematol 17:805–808, 1989.

28. Osband ME, Ross S: Problems in the investigational study and clinical use of cancer immunotherapy. Immunol Today 11:193–195, 1990.
29. Johnson CS: Interleukin-1: Therapeutic potential for solid tumors. Cancer Invest 11:600–608, 1993.
30. Wang Z, Sinha BK: Interleukin-1 alpha-induced modulation of topoisomerase I activity and DNA damage: Implications in the mechanisms of synergy with camptothecins in vitro and in vivo. Mol Pharmacol 49:269–275, 1996.
31. Logan TF, Bishop H, Mintun MA, Choi Y, Sashin D, Virji MA, et al.: Phase I trial of interleukin-1 alpha and carboplatin in patients with metastatic disease to the lung: Effects on tumor blood flow evaluated by positron emission tomography (meeting abstract). Proc Annu Meet Am Assoc Cancer Res 35:A1183, 1994.
32. Schuchter L, Neuberg D, Atkins M, Tester B, Recio A, Sickles C, et al.: A phase I study of interleukin-1 alpha (IL-1) and high dose cyclophosphamide (Cy) in patients with advanced cancer (meeting abstract). Proc Annu Meet Am Soc Clin Oncol 13:A327, 1994.
33. Kilbourn RG, Gross SS, Lodato RF, Adams J, Levi R, Miller LL, et al.: Inhibition of interleukin-1-alpha-induced nitric oxide synthase in vascular smooth muscle and full reversal of interleukin-1-alpha-induced hypotension by N omega-amino-L-arginine. J Natl Cancer Inst 84:1008–1016, 1992.